The present invention is directed to antibodies which bind with amino acid sequences of HIV-1 corresponding to ORF-Q, ORF-R, ORF-1, ORF-2, and ORF-4; antibodies which bind with immunological complexes comprising an amino acid sequence of HIV-1 corresponding to ORF-Q, ORF-R, ORF-1, ORF-2, or ORF-4; and immunological complex comprising an amino acid sequence of HIV-1 corresponding to ORF-R, ORF-1, ORF-2, or ORF-4.

The Examiner rejected the claims for lack of utility because the ORF regions recited in the claims

> have not been shown to be expressed in biological samples, and there is no practical utility associated with screening for peptides which do not occur in nature, especially with respect to HIV related peptides.

Office Action at 2. Applicants disagree.

Because the ORF regions recited in the claims encode proteins of HIV-1, the claimed invention has utility. Specifically, ORF-Q corresponds to *vif* protein, ORF-R corresponds to *nef* protein, ORF-1 corresponds to *vpr* protein, ORF-2 corresponds to *tat* protein, and ORF-4 corresponds to *vpu* protein of HIV-1.

ORF-Q, or *vif* (virion infectivity factor), is also known as *sor*, *A*, *P'*, and *Q*. See Gallo et al., "HIV/HTLV Gene Nomenclature," Nature, 333, page 504 (1988) (Exhibit 1). This protein is referred to as "ORF-1" in Sanchez-Pescador et al.,

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"Nucleotide Sequence and Expression of an AIDS-Associated Retrovirus (ARV-2)," Science, 227, 484-492, 491 (1985) (Exhibit 2). This reference notes that ORF-1 (*i.e., vif*) has a potential start codon at the 5' end of the open reading frame, and that the ORF is located in the region which is expressed as a protein implicated in viral pathogenesis for HTLV-1 and HTLV-2. See Sanchez-Pescador et al. at 491.

ORF-R, or *nef* (negative factor), is also known as *3'orf*, *B*, *E'*, and *F*. ORF-2 or *tat* (transactivator), is also known as *tat-3* and *TA*. See Gallo et al.

The immune reactivity of *vif*, *nef*, and *tat* is described by Arya et al., "Three Novel Genes Of Human T-lymphotropic Virus Type III: Immune Reactivity Of Their Products With Sera From Acquired Immune Deficiency Syndrome Patients," Proc. Natl. Acad. Sci. USA, 83, 2209-2213 (1986) (Exhibit 3). This reference refers to *vif* as *sor* and *nef* as *3'orf*. Experimental results showed that proteins corresponding to *vif*, *tat*, and *nef* are immune reactive and immunogenic in the natural host. The results also showed that the genes coding for the three proteins of HIV-1 function *in vivo*. Abstract of Arya et al.

The protein encoded by the *tat* gene of HIV-1 is further characterized by Arya et al., "*Trans*-Activator Gene of Human T-Lymphotropic Virus Type III (HTLV-III)," Science, 229, 69-73 (1985) (Exhibit 4). This reference teaches that the protein encoded by the *trans* or *tat* gene activates the expression of LTR-linked genes.

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The HIV-1 genes *tat* and *nef* are also described by Schwartz et al., "Cloning And Functional Analysis Of Multiply Spliced mRNA Species Of Human Immunodeficiency Virus Type 1," Journal of Virology, 64, 2519-2529 (1990) (Exhibit 5). Fig. 5 of this reference describes immunoprecipitation of *tat* and *nef* proteins expressed from cDNA clones. Schwartz et al. at 2525.

ORF-4, or *vpu*, is described by Cohen et al., "Identification Of A Protein Encoded By The *vpu* Gene Of HIV-1," Nature, 334, 532-534 (1988) (Exhibit 6), and Strebel et al., "A Novel Gene of HIV-1, *vpu*, And Its 16-Kilodalton Product," Science, 241, 1221-1223 (1988) (Exhibit 7). Cohen et al. teach antibody recognition to peptides corresponding to *vpu* in rabbits and the ability of human antiserum to precipitate protein products of *vpu*. Cohen et al. at 532-533. This reference also teaches that *vpu* is highly conserved among the isolated HIV-1 proviral sequences. Cohen et al. at 534.

Strebel et al. teach that *vpu* protein of HIV-1 reacted with about one third of the tested serum samples from AIDS patients, which indicates that the *vpu* ORF is expressed *in vivo* as well as in *in vitro*. Abstract of Strebel et al.

Finally, ORF-1, or *vpr*, is described by Wong-Staal et al., "Human Immunodeficiency Virus: The Eighth Gene," AIDS Research and Human Retroviruses, 3, 33-39 (1987) (Exhibit 8). Wong-Staal et al. refer to *vpr* as the "R gene." Table 1 of this reference indicates the prevalence of antibodies against the *vpr* gene

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product in HIV-1 infected patients. This reference also notes that *vpr* is highly conserved among HIV-1 isolates. Wong-Staal et al. at 34. Additional serological detection by patient sera of the *vpr* protein of HIV-1 is described in Fig. 2 at page 37 of Wong-Staal et al.

Wong-Staal et al. also describe the serological reactivity of proteins encoded by *vif* (or *sor*) and *nef* proteins of HIV-1. Wong-Staal et al. at 33.

Because the ORFs recited in the claimed invention encode proteins capable of being immunologically recognized by biological sera, the claimed invention has utility. Withdrawal of this ground for rejection is respectfully requested.

Applicants acknowledge that this application is under final rejection. However, because this response is believed to place the application in condition for allowance, applicants respectfully request entry thereof by the Examiner.

Reexamination and reconsideration of this application, and allowance of the pending claims at the Examiner's convenience, are respectfully requested.

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If there are any fees due in connection with the filing of this Response, please charge such fees to our Deposit Account No. 06-0916. If a fee is required for an Extension of Time under 37 C.F.R. § 1.136 not accounted for above, such an Extension is requested and fee should also be charged to our Deposit Account.

Respectfully submitted,

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Dated: August 4, 1994

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